



Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Panel's Recommendations

I. Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?

- The prevention of influenza in children with HIV aged ≥ 6 months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) (**strong, moderate**).
- Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccine^a (e.g., intranasal administered influenza vaccine, FluMist) (**weak, very low**).
- Household members and close contacts (aged ≥ 6 months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) (**strong, moderate**).

II. Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?

- Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 T lymphocyte [CD4] cell percentage $<15\%$) while influenza virus is circulating in the community, after careful consideration of risks and benefits as outlined in Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines (**weak, low**).
- Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage $<15\%$), regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza (**strong, moderate**).
- Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable (**strong, moderate**) or in seasons in which low influenza vaccine effectiveness is documented (**strong, low**), if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.

III. Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?

- Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should be given without waiting for confirmatory laboratory testing and without regard to illness duration (**strong, moderate**). Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients (**weak, low**).
- Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible (**strong, moderate**). Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.
- In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged >5 years, and has no other underlying condition that places the child at high risk of complications from influenza (**weak, low**).

Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

^a As of the 2017–2018 influenza season, live attenuated influenza vaccine (LAIV) is **not recommended** by ACIP for any pediatric or adult patient given concerns about effectiveness. Please see the most recent ACIP statements regarding use of LAIV in future seasons.

Epidemiology

Influenza viruses are spread directly from person to person across distances up to 6 feet via large or small droplets generated by coughing or sneezing, or indirectly from contaminated surfaces to hands to mucosal membranes.¹ Influenza has an incubation period of 1 to 4 days (mean: 2 days),² and can be shed by adults from 1 day before to 5 to 7 days after onset of symptoms and by children from several days before to ≥ 10 days after illness onset.³ Viral shedding can occur over longer periods in those with chronic diseases,

including patients with immunosuppression or those receiving systemic corticosteroid therapy.⁴⁻⁷

Seasonal influenza viruses can be divided into three types: A, B, and C. Influenza A viruses are further subdivided based on surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Influenza A viruses circulate primarily among aquatic birds, but also among humans and other animals, including pigs, horses, and seals. Influenza A virus subtypes H1N1pdm09 and H3N2 currently circulate among humans. Influenza B viruses circulate primarily among humans.⁸ Influenza C viruses circulate primarily among animals such as swine and dogs but are increasingly appreciated in humans.⁹⁻¹² Influenza A and B, but not C, cause seasonal outbreaks. Surveillance and immunization are currently performed for influenza A and B. Two influenza A subtypes (one H1N1 and one H3N2); and one influenza B strain for trivalent vaccine formulations, or two influenza B strains for quadrivalent vaccine formulations are included in current seasonal influenza vaccines. In the United States, influenza viruses cause annual outbreaks lasting from winter through spring.

The Centers for Disease Control and Prevention (CDC) has identified certain groups to be at risk of complications from influenza, including individuals with immunosuppression caused by HIV infection.¹³ The burden of influenza virus in children with HIV has been characterized in limited case reports and case series, but assessment of its impact has been confounded by the stage of HIV infection, type of antiretroviral therapy (ART), and other comorbidities.¹⁴ In the era before the availability of combination antiretroviral therapy (cART), multiple large epidemiological studies suggested high hospitalization and mortality rates associated with influenza in individuals with HIV.^{15,16} However, observations reported during the cART era suggest that better control of HIV infection is associated with a milder course of influenza. In an outbreak of pandemic 2009 H1N1 influenza in Germany involving ¹⁵ schoolchildren with HIV receiving cART, the clinical course of influenza in children with HIV was similar to that in children without HIV.¹⁷ A case series of 13 children with HIV with pandemic 2009 H1N1 in Barcelona in 2009 also reported outcomes similar to those in groups without HIV.¹⁸ In both reports, half of the children were aged <13 years, had CD4 T lymphocyte (CD4) counts >500 cells/mm³, and had very low or undetectable HIV viral loads. Recent adult data suggest that, despite the introduction of ART, influenza-related mortality in adults with AIDS is still greater than in the general population.¹⁹ Further, using national mortality and laboratory surveillance data from 1998–2009, a study from South Africa reported that the risk of death associated with influenza in children aged <5 years was greater in children with HIV than in those without HIV (RR 11.5, 95% CI, 9.6–12.6).²⁰ Large prospective, observational studies of children with HIV are needed to further substantiate these findings.

Clinical Manifestations

Signs and symptoms related to influenza are similar in children with and without HIV and include fever, cough, and rhinorrhea in the majority of patients.^{17,18,21} Loss of appetite was more common in patients with HIV than in patients without HIV in one study.²² In a prospective cohort study of hospitalized children with laboratory-confirmed influenza conducted in South Africa from 1997 to 1999, prior to cART availability, radiographic evidence of alveolar consolidation was more frequent in children with HIV than in children without HIV. Clinical outcomes including duration of hospitalization and in-hospital mortality were similar for both children with and without HIV.²² In one small study conducted during the 2009 H1N1 pandemic, chest radiography patterns differed with HIV status; children with HIV were more likely to have an interstitial infiltrate and children without HIV more likely to have a consolidative infiltrate. Children with HIV were also more likely to have leukopenia associated with their influenza diagnosis than children without HIV.²³

Diagnosis

The laboratory approach to diagnosis of influenza in children with and without HIV is identical. This includes rapid influenza diagnostic tests (RIDTs), immunofluorescence assays, reverse transcription-polymerase chain reaction (RT-PCR) assays, and viral culture. RT-PCR and viral culture are considered the gold standard influenza tests. Viral culture has lower sensitivity than RT-PCR and results are not immediately available. RIDTs offer point-of-care diagnosis, but sensitivity is substantially lower than for viral culture or

RT-PCR, which makes false-negative results a significant concern in clinical application. In addition RIDTs can be falsely positive when the prevalence of influenza is low, thus limiting their reliability for patient management in both high and low prevalence seasons.²⁴ Clinical diagnosis with laboratory confirmation of influenza is important, especially for hospitalized patients and outpatients at higher risk of influenza complications. Molecular diagnostic methods (e.g., RT-PCR) offer the most sensitive and specific diagnostic testing and can be performed at many specialized laboratories, such as hospital laboratories, commercial referral laboratories, and county and state public health laboratories.

Prevention Recommendations

Preventing Exposure

Basic personal hygiene, including hand hygiene and proper cough etiquette, are mainstays of influenza prevention. Individuals should avoid touching their eyes, nose, and mouth and avoid contact with sick individuals. Hands should be washed often with soap and water or, if soap and water are unavailable, with an alcohol-based hand rub containing at least 60% alcohol. Proper hand washing technique involves wetting hands with clean running water, applying soap, and rubbing and scrubbing all hand surfaces and under the fingernails for at least 20 seconds. Hands should be dried with a clean towel or air dried. When using alcohol-based hand rub, the hand rub should be applied to one hand, and the hands (including all hand surfaces and fingers) should be rubbed together until dry.

Cough etiquette directs that individuals cough or sneeze into a tissue rather than into their hands. A soiled tissue should be disposed of in a waste basket. Measures used by public health authorities during influenza pandemics include recommendations to reduce crowding, to maintain a few feet of distance from others, to avoid shaking hands or hugging at gatherings, and to avoid gatherings altogether (see [Preventing the Flu: Good Health Habits Can Help Stop Germs](#) and [Handwashing: Clean Hands Save Lives](#)).

Prolonged influenza viral replication in immunocompromised patients has implications for spread of influenza in the health care setting, as well as in the community. Immunocompromised patients with prolonged viral replication in the respiratory tract could potentially serve as a reservoir for spread of influenza in the hospital and the community. In addition, prolonged viral replication increases the risk for emergence of antiviral resistance if antiviral exposure occurs. Strategies to prevent the spread of influenza in health care facilities include use of standard and droplet precautions by health care workers, as well as caution when performing aerosol-generating procedures according to [Healthcare Infection Control Practices Advisory Committee guidelines](#).²⁵

In addition to the above measures, influenza prevention efforts for children with HIV also include vaccinating the children's close contacts and limiting spread of influenza from household members. Household members may be vaccinated with any medically appropriate vaccine formulation. Though not recommended for the 2017–2018 season, live attenuated influenza vaccine (LAIV) is considered safe for household contacts of children with HIV if the contacts fulfill criteria for LAIV receipt. Isolation of household members with any acute respiratory illness from the child with HIV, prompt influenza testing, and presumptive antiviral treatment in potentially infected household members are additional tools to prevent spread of influenza to children with HIV.

Preventing First Episode of Disease

Annual influenza vaccination is a cornerstone of influenza prevention at both the individual and community level.²⁶ Past concerns about an increase in HIV viral load following influenza vaccination have not been substantiated, particularly in individuals on ART.^{13,27–31} Currently in the United States, inactivated influenza vaccine (IIV) is recommended for patients with HIV according to the CDC Advisory Committee on Immunization Practices (ACIP) guidelines. Studies examining the immune response of children and adolescents with HIV on ART to inactivated influenza vaccination have generally shown immune responses comparable to those seen in individuals without HIV.³² Children with HIV-related immunologic

impairment or with symptomatic HIV demonstrate decreased immune responses to influenza vaccination (see [Recommendation Table](#)). High-dose IIV was recently studied in a small cohort of children and young adults with HIV, though it was not significantly more immunogenic in these patients than standard-dose IIV.³³ Additional studies of high-dose IIV in populations at increased risk for influenza are in progress. LAIV **is not recommended** for immunosuppressed persons per CDC/ACIP guidance.³⁴ Furthermore, current Infectious Diseases Society of America (IDSA) guidelines for LAIV immunization of immunocompromised persons state that LAIV **should not be administered** to immunocompromised persons or persons with HIV.³⁵ Some experts would consider using LAIV (which may remain available) in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV who meet these conditions.³⁶ However, the CDC/ACIP and IDSA guidelines recommend against such practice, and LAIV is not licensed for use in children with HIV. Further, LAIV is not currently recommended by ACIP for all populations because of decreased effectiveness.

Contraindications to the use of inactivated influenza vaccines are few and are the same for individuals with and without HIV. Influenza vaccines **are not approved** for children aged <6 months. Per CDC/ACIP guidance, persons with a previous severe allergic reaction to influenza vaccine **should not receive influenza vaccine in the future**.³⁴ Future avoidance of influenza vaccine in this setting is recommended regardless of the component suspected of being responsible for the reaction. Persons who report having had egg-associated reactions involving symptoms other than hives (e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention, may receive any licensed and recommended influenza vaccine “that is otherwise appropriate for the recipient’s age and health status.”³⁴ In persons with severe egg reactions, influenza vaccine should be administered in an inpatient or outpatient medical setting with supervision by a health care provider able to recognize and manage severe allergic conditions.³⁴ A physician should be consulted before influenza vaccine is administered to children who have a moderate-to-severe illness with a fever (in which case, vaccination should be postponed until the child recovers).

Options for antiviral chemoprophylaxis of influenza include antiviral administration in the pre- or post-exposure setting to children and adolescents with HIV (see Panel Recommendations above). Pre-exposure prophylaxis should rarely be used, except in persons who are severely immunocompromised and therefore at very high risk for influenza virus-associated morbidity and mortality during periods of greatly increased risk for influenza exposure.³⁷ The choice to provide post-exposure prophylaxis to an individual patient depends on the patient’s state of immunosuppression and immunization status, as well as the seasonal vaccine effectiveness depending on the vaccine match with the circulating strains of influenza (See Panel Recommendations above and Evidence Summary below).³⁷ Selection of an antiviral drug for chemoprophylaxis should be based on current CDC/ACIP influenza antiviral recommendations and take into consideration the weekly antiviral susceptibility testing data for the circulating influenza virus strains that is provided by CDC (see [Weekly U.S. Influenza Surveillance Report](#) or [FluView](#)). Post-exposure antiviral chemoprophylaxis should be started within 48 hours of exposure to a contact with confirmed or suspected influenza. Oseltamivir and zanamivir, which are members of the antiviral class of medications called neuraminidase inhibitors, are approved and are recommended for chemoprophylaxis against influenza A and B viruses in children. Oseltamivir prophylaxis is not Food and Drug Administration (FDA)-approved for children aged <1 year, but the American Academy of Pediatrics (AAP) and CDC have issued recommendations for prophylaxis of children aged ≥3 months; zanamivir prophylaxis is not recommended for children aged <5 years (see table below). Although oseltamivir resistance has been documented previously among circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) circulating influenza A and B viruses have been susceptible to oseltamivir.^{37,38} Amantadine and rimantadine, adamantane derivatives which only have activity against influenza A viruses, are approved but not currently recommended for chemoprophylaxis of influenza A virus infection because of widespread resistance of current influenza A (H3N2 and H1N1pdm09) virus strains to adamantanes.^{37,39}

Discontinuing Primary Prophylaxis

Though used only rarely, when a pre-exposure chemoprophylaxis strategy is employed, antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community.³⁷

The recommended duration of post-exposure chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child's degree of immunosuppression and the degree of match with circulating influenza viruses.^{37,40} If influenza vaccination is provided after contact, chemoprophylaxis duration should generally be 2 weeks after vaccination. If exposure is to a household contact, chemoprophylaxis duration should be 7 days (see [Influenza Antiviral Medications: Summary for Clinicians](#)). If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days, or 7 days after onset of symptoms in the last person infected, whichever is longer. The duration of chemoprophylaxis after other exposure types should generally be 7 days.

Treatment Recommendations

Treating Disease

Treatment of influenza in children with HIV is recommended according to CDC/ACIP guidelines. The recommended duration of treatment is 5 days, but may need to be extended in severely ill hospitalized or immunocompromised patients.⁴⁰⁻⁴³ As with primary chemoprophylaxis, selection of an antiviral drug for treatment should be based on current CDC/ACIP influenza antiviral recommendations and should account for antiviral susceptibility testing data for circulating influenza virus strains that is provided by CDC (see [Weekly U.S. Influenza Surveillance Report](#) or [FluView](#)). Currently recommended influenza antiviral medications are the neuraminidase inhibitor drugs, oseltamivir (orally administered), zanamivir (inhaled), and peramivir (intravenous). Peramivir is approved for treatment in persons aged ≥ 18 years. All three are effective for treatment against influenza A and B viruses. Oseltamivir is FDA-approved for treatment of influenza in children aged ≥ 2 weeks; however, both CDC and AAP recommend the use of oral oseltamivir for treatment of influenza in infants aged < 2 weeks when needed (see [Influenza Antiviral Medications: Summary for Clinicians](#)).⁴³

Although oseltamivir resistance was documented in circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) of circulating influenza A and B viruses have been susceptible to oseltamivir.^{37,38} Zanamivir is approved for treatment of influenza in children aged ≥ 7 years (see Table below). Peramivir, though FDA-approved only for treatment of persons aged ≥ 18 years, has been studied in pediatric populations.⁴⁴⁻⁴⁶ Importantly, the most common neuraminidase inhibitor mutation (H275Y) imparts resistance to both oseltamivir and peramivir.^{47,48} Adamantanes (rimantadine, amantadine) have activity only against influenza A viruses, but are not currently recommended for treatment of influenza A because of resistance of currently circulating influenza A (H3N2 and H1N1pdm09 virus strains).^{37,39}

Monitoring of Adverse Events

Clinicians should take into account patients' age, weight, renal function, history of seizures, level of immunosuppression, other medical conditions, and potential drug interactions when considering administration of influenza antiviral medications and evaluating their associated adverse events.³⁷

Oseltamivir: In studies in adults and children, mild nausea and vomiting have been the most common side effects of treatment with oseltamivir;^{49,50} however, these symptoms can be reduced if the medication is taken with food.⁵¹ Despite earlier post-market reports from Japan of transient neuropsychiatric events manifested as self-injury or delirium, oseltamivir has not been reproducibly associated with increased risk of neuropsychiatric events.⁵² Moreover, influenza infection itself is associated with neurologic complications such as febrile seizures, encephalopathy, and encephalitis. FDA recommends close monitoring for

abnormal behavior in patients treated with oseltamivir.⁵¹ FDA and CDC also recommend that clinicians and pharmacists pay careful attention to avoid dosing errors in young children.⁵³

Zanamivir: Because of cases of respiratory deterioration manifested as decreased forced expiratory volume or bronchospasm in patients with asthma or chronic obstructive pulmonary disease receiving zanamivir, this agent **is not recommended** for treatment of influenza in patients with underlying pulmonary disease. In clinical treatment studies involving patients with uncomplicated influenza, common adverse events were similar in those treated with inhaled zanamivir and those treated with inhaled placebo.^{37,41}

Drug Interactions: Clinical data are limited with respect to drug interactions between influenza antiviral drugs and antiretroviral (ARV) drugs, and no clinical trials to date have evaluated the safety or efficacy of using combinations of different classes of influenza antiviral drugs.³⁷ However, information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions with ARV agents are unlikely. Moreover, since none of the neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) affect cytochrome P450 (CYP450) isoenzymes, no clinically significant drug interactions are predicted based on *in vitro* studies.

Managing Treatment Failure (Influenza Disease Progression)

Clinicians developing management plans in response to treatment failure or severe illness associated with influenza viral infections can consider changing antiviral dosing or route of administration, increasing duration of therapy, or tailoring therapy based on viral resistance.⁴⁰ The potential use of increased oseltamivir doses in critically ill patients has emerged from concerns surrounding enteric absorption of oseltamivir in this patient population, but these concerns have not been substantiated in clinical trials. One small study demonstrated therapeutic plasma levels of oseltamivir in critically ill adult patients comparable to those seen in ambulatory adult patients.⁵⁴ In addition, a prospective study from Hong Kong showed no overall clinical or virologic benefit of higher dose as compared to standard dose oseltamivir in hospitalized adults, though a trend to more rapid viral clearance of influenza B, but not of influenza A, was noted in a sub-analysis.⁵⁵ Patients who are severely ill and hospitalized or who are immunosuppressed may require longer treatment with oseltamivir.⁴⁰ For hospitalized children or those with severe disease, treatment with inhaled zanamivir is not recommended because evidence for its use in this setting is lacking. In December 2014, FDA approved intravenous (IV) peramivir for treatment of acute uncomplicated influenza in persons aged ≥ 18 years. Although not licensed for children, pediatric use of peramivir is reported and off-label use could be considered in severely ill children, especially those patients who cannot tolerate or absorb oral/enteral oseltamivir. Expert opinion supports consideration of IV peramivir use in hospitalized children aged ≥ 2 years and adults or those with severe disease, although efficacy in this setting has not been demonstrated.^{40,44} Further studies to support its safety and efficacy are needed.^{45,56,57}

Prior to the 2017–2018 influenza season, IV zanamivir was available through clinical trial enrollment or via an Emergency Investigational New Drug application for settings in which oseltamivir-resistant influenza virus infection was suspected or confirmed (see [Influenza Antiviral Medications: Summary for Clinicians](#)). However, at present IV zanamivir is no longer available in the United States. Importantly, as noted above, if oseltamivir-resistant influenza virus infection is suspected or confirmed, peramivir is not indicated because of demonstrated cross-resistance between oseltamivir and peramivir.

Preventing Recurrence

See sections Preventing Exposure and Preventing First Episode of Disease.

Discontinuing Secondary Prophylaxis

Not applicable.

Primary Prevention

1. Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?

- i. Prevention of influenza in children with HIV aged ≥ 6 months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) (**strong, moderate**). This recommendation is based on review of IDSA,³⁵ CDC/ACIP,³⁴ and AAP⁴³ guidelines.

Annual influenza vaccination is universally recommended for all children aged ≥ 6 months.³⁴ Studies of influenza vaccination in children with HIV have generally shown that influenza vaccination is safe and immunogenic. Some studies have demonstrated that, compared to children without HIV, children with HIV have decreased antibody responses to influenza vaccination.⁵⁸⁻⁶¹ Others have shown that children with HIV with greater immune impairment or a more symptomatic clinical stage had decreased immune response to influenza vaccination.^{62,63} Despite this potential for modestly impaired immune response to influenza vaccination in children with HIV, seroprotection (i.e., hemagglutination inhibition [HAI] antibody titer $\geq 1:40$) was achieved in up to 92% of vaccine recipients⁶⁴ and seroconversion (≥ 4 -fold rise in post-vaccine HAI titer as compared to pre-vaccine HAI titer) in as many as 85% of vaccine recipients⁶⁵ in studies of children with HIV.

In one randomized, double-blind, placebo controlled trial of influenza vaccination in children with HIV, immune responses were measured by HAI and vaccine efficacy was determined using active surveillance data.⁶⁶ Seroprotection among the vaccinated population was low and vaccine efficacy was only 17.7% (95% CI, 0% to 62.5%). Importantly, 92% of participants in this study were receiving ART and the median CD4 percentage was 33.5 (range: 15.2% to 55.9%). However, in a similar study performed in adults with HIV in the same setting, vaccine efficacy was 75.5% (95% CI, 9.2% to 95.6%).⁶⁷ Thus, given the CDC/ACIP recommendation for universal influenza vaccination in children aged ≥ 6 months and the potential for protection against influenza by administration of influenza vaccination, yearly administration of influenza vaccine to children with HIV is strongly advised.

- ii. Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccines (intranasal administered influenza vaccine, FluMist) (**weak, very low**). This recommendation is based on review of the IDSA guideline for vaccination in the immunocompromised host.³⁵

Several studies have evaluated LAIV administration to children and/or adults with HIV.^{68,36,69,60,70} In these studies, LAIV administration was safe and not associated with serious adverse events. In most of these studies, individuals with HIV were not significantly immunocompromised at the time of study vaccination. Although some experts would consider using LAIV in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV meeting these conditions,³⁶ current IDSA guidelines for immunization of immunocompromised hosts recommend against immunization of children, adolescents, and adults with HIV with LAIV.³⁵

- iii. Household members and close contacts (aged ≥ 6 months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) (**strong, moderate**).

Annual influenza vaccination is universally recommended for all adults and children aged ≥ 6 months.^{34,71} Given the immunocompromised state of children with HIV and the potential for impaired immune response to influenza vaccination, special emphasis on vaccination of those persons in

household and/or close contact with children with HIV is warranted. Ensuring that household/close contacts are vaccinated against influenza likely provides additional prevention against influenza in children with HIV. While there are no specific studies addressing a “cocoon” strategy for influenza prevention in children with HIV, this recommendation is in accordance with universal influenza vaccination recommended by CDC/ACIP.

2. Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?

- i. Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 percentage <15%) while influenza virus is circulating in the community (**weak, low**). Use of this strategy requires careful consideration of risks and benefits and attention to influenza circulation as outlined in CDC/ACIP,³⁷ IDSA,⁴² and AAP⁴³ guidelines.
- ii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage <15%) regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza (**strong, moderate**).
- iii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable (**strong, moderate**) or in seasons in which low influenza vaccine effectiveness is documented (**strong, low**) if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.

No antiviral chemoprophylaxis studies for prevention of influenza have been specifically performed in children with HIV. These recommendations were made with reference to current guidelines on antiviral chemoprophylaxis against influenza published by the CDC/ACIP, IDSA, and AAP. In severely immunosuppressed children, influenza vaccination may be poorly immunogenic. Therefore, antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression regardless of vaccination status.

Post-exposure antiviral chemoprophylaxis should be given **only** if it can be started within 48 hours after the initial exposure **and** if the recipient is asymptomatic. If more than 48 hours have elapsed since the initial exposure, then either no chemoprophylaxis should be given, or the treatment antiviral dose should be given. If the potential recipient is already symptomatic, prompt antiviral treatment should be initiated (see Clinical Question #3). Use of prophylactic once-daily dosing in the setting of active viral replication poses a risk of emergence of antiviral resistance.⁷²⁻⁷⁵ Further information regarding antiviral chemoprophylaxis can be found at [Influenza Antiviral Medications: Summary for Clinicians](#).

Treatment

3. Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?

- i. Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should

be given without waiting for confirmatory laboratory testing and without regard to illness duration (**strong, moderate**). Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients (**weak, low**).

- ii. Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible (**strong, moderate**). Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.
- iii. In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged >5 years, and has no other underlying condition that places the child at high risk of complications from influenza (**weak, low**).

No antiviral treatment studies have been specifically performed in children with HIV with influenza. The recommendations are made with reference to current influenza chemoprophylaxis and treatment guidelines published by CDC/ACIP,³⁷ IDSA,⁴² and AAP.⁴³ Further information regarding antiviral treatment can be found at [Influenza Antiviral Medications: Summary for Clinicians](#).

Secondary Prevention

Not applicable.

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Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza

Indication	First Choice	Alternative	Comments/Special Issues
Primary Chemoprophylaxis (Pre- and Post-Exposure) Influenza A and B	<p><u>Oseltamivir</u></p> <ul style="list-style-type: none"> • Aged <3 Months: Not recommended^a • Aged 3 Months to <1 Year: Oseltamivir 3 mg/kg body weight/dose once daily^a • Aged ≥1 to 12 Years: Weight-band dosing^a <ul style="list-style-type: none"> • Weighing ≤15 kg: Oseltamivir 30 mg once daily • Weighing >15 kg to 23 kg: Oseltamivir 45 mg once daily • Weighing >23 kg to 40 kg: Oseltamivir 60 mg once daily • Weighing >40 kg: Oseltamivir 75 mg once daily • Aged ≥13 Years: Oseltamivir 75 mg once daily <p><u>Zanamivir (Aged ≥5 Years):</u></p> <ul style="list-style-type: none"> • Zanamivir 10 mg (2 inhalations) once daily^b 	None	<p><u>Pre-Exposure Chemoprophylaxis</u></p> <p><i>Indications:</i></p> <ul style="list-style-type: none"> • After careful consideration of risks and benefits, pre-exposure antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression while influenza virus is circulating in the community. <p><i>Duration:</i></p> <ul style="list-style-type: none"> • When employed, pre-exposure antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community. <p><u>Post-Exposure Chemoprophylaxis</u></p> <p><i>Indications Recommended For:</i></p> <ul style="list-style-type: none"> • Children with HIV with severe immunosuppression regardless of influenza vaccination status. • Children with HIV with moderate to no immunosuppression if <ul style="list-style-type: none"> • Influenza vaccination is contraindicated or unavailable; or • Low influenza vaccine effectiveness is documented in the current influenza season; and • Antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza. <p><i>Duration:</i></p> <p>Note: Duration of chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child's degree of immunosuppression and the degree of match with circulating influenza viruses.</p> <ul style="list-style-type: none"> • If influenza vaccination is provided after contact, chemoprophylaxis duration should be 2 weeks after vaccination. • If exposure is to a household contact, chemoprophylaxis duration should be 7 days. • If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days or 7 days after onset of symptoms in the last person infected, whichever is longer.^c <p><u>Oseltamivir Dosing Adjustments</u></p> <p><i>Premature Infants:</i></p> <ul style="list-style-type: none"> • Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).^d <p><i>Renal Insufficiency:</i></p> <ul style="list-style-type: none"> • A reduction in dose of oseltamivir is recommended for patients with CrCl <30 mL/min. For patients with CrCl 10–30 mL/min, a reduction in chemoprophylaxis dosing frequency to every other day is recommended. Pharmacokinetic data are limited for dosing recommendations for patients with severe renal insufficiency on dialysis.

Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Chemoprophylaxis	N/A	N/A	No role for secondary chemoprophylaxis
Treatment Influenza A and B	<u>Oseltamivir:</u> ^e <ul style="list-style-type: none"> • Aged <3 Months: Oseltamivir 3 mg/kg/dose twice daily • Aged 3 Months to <1 Year: Oseltamivir 3 mg/kg/dose twice daily • Aged ≥1 to 12 Years: Weight-band dosing <ul style="list-style-type: none"> • Weighing ≤15 kg: Oseltamivir 30 mg twice daily • Weighing >15 kg to 23 kg: Oseltamivir 45 mg twice daily • Weighing >23 kg to 40 kg: Oseltamivir 60 mg twice daily • Weighing >40 kg: Oseltamivir 75 mg twice daily • Aged ≥13 Years: Oseltamivir 75 mg twice daily <u>Zanamivir (Aged ≥7 Years):</u> <ul style="list-style-type: none"> • Zanamivir 10 mg (2 inhalations) twice daily^f 	None	<p><i>Duration:</i></p> <ul style="list-style-type: none"> • The recommended antiviral treatment duration for either oseltamivir or zanamivir is 5 days. Per CDC recommendations, longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.^c <p><u>Oseltamivir Dosing Adjustments</u></p> <p><i>Premature Infants:</i></p> <ul style="list-style-type: none"> • Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery <38 weeks).^d <p><i>Renal Insufficiency:</i></p> <ul style="list-style-type: none"> • Oseltamivir renal dosing is not well established for pediatric patients. For children >40 kg, adult renal dosing can be used. <p><u>CrCl/Dose:</u></p> <ul style="list-style-type: none"> • 61–90 mL/minute: 75 mg twice daily • 31–60 mL/minute: 30 mg twice daily • 11–30 mL/minute: 30 mg once daily • ≤10 mL/minute, ESRD on hemodialysis: 30 mg dose after every hemodialysis cycle • ≤10 mL/minute, ESRD continuous ambulatory peritoneal dialysis: single 30 mg dose administered after a dialysis exchange

^a Oseltamivir is FDA-approved for prophylaxis of influenza in children aged ≥1 year. It is not approved for prophylaxis in children aged <1 year. However, CDC recommends that health care providers who treat children aged ≥3 months to <1 year administer a chemoprophylaxis dose of oseltamivir 3 mg/kg body weight/dose once daily. Chemoprophylaxis for infants aged <3 months **is not recommended** unless the exposure situation is judged to be critical.

^b Zanamivir **is not recommended** for chemoprophylaxis in children aged <5 years or for children with underlying respiratory disease.

^c See Fiore 2011 and [Influenza Antiviral Medications: Summary for Clinicians](#) for further details.

^d See Acosta et al. *J Infect Dis* 2010; 202:563-566 for dosing recommendations in premature infants.

^e Oseltamivir is FDA-approved for treatment of influenza in children aged ≥2 weeks; however, both CDC and AAP recommend use of oral oseltamivir for influenza treatment in infants aged <2 weeks.

^f Zanamivir **is not recommended** for treatment in children aged <7 years or for children with underlying respiratory disease.

Key to Acronyms: AAP = American Academy of Pediatrics; CDC = Centers for Disease Control and Prevention; CrCl = creatinine clearance; ESRD = end stage renal disease; FDA = Food and Drug Administration; PK = pharmacokinetic